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Depth and Patterns of Adnexal Involvement in Primary Extramammary (Anogenital) Paget Disease: A Study of 178 Lesions From 146 Patients

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Abstract: Extramammary Paget disease (EMPD) is a rare neoplasm usually presenting in the anogenital area, most commonly in the vulva. Adnexal involvement in primary EMPD is a very common feature and serves as a pathway for carcinoma to spread into deeper tissue. The depth of carcinomatous spread along the appendages and the patterns of adnexal involvement were studied in 178 lesions from 146 patients with primary EMPD. Hair follicles and eccrine ducts were the adnexa most commonly affected by carcinoma cells. The maximal depth of involvement was 3.6 mm in this series. When planning topical therapy or developing novel local treatment modalities for EMPD, this potential for significant deep spread along adnexa should be taken into account.

Key Words: extramammary Paget disease, adnexa, invasion, vulva

(*Am J Dermatopathol* 2016;38:802–808)

INTRODUCTION

Extramammary Paget disease (EMPD) is a rare neoplasm usually presenting in the anogenital area, most commonly in the vulva, where it represents approximately 1% of malignant lesions.[1] EMPD can be divided into primary and secondary variants, the latter representing intraepithelial spread of an underlying carcinoma, usually from the urogenital or gastrointestinal tracts.[2–5]

Primary EMPD is a form of intraepithelial adenocarcinoma of uncertain histogenesis, for which cutaneous adnexa, clear cells of Toker, pluripotent stem cells, and anogenital mammary-like glands (AGMLG) have been proposed as possible sites of origin.[2,6–18]

Surgical excision is a widely used treatment modality for primary EMPD but this can be disfiguring and recurrences are not uncommon. Other than surgery, in recent years, topical drugs such as imiquimod, 5-fluorouracil, and retinoic acid, alone or in combination, have been used for the treatment of EMPD.[19] The application of these drugs is based on the premise that most primary EMPD represents a form of adenocarcinoma in situ, in which a proliferation of the neoplastic cells is confined to the epidermis or mucosal epithelium and can be destroyed by the drug, either directly or through immunoreactive processes. One can speculate, however, that in EMPD invading the underlying dermis, these treatments would be less effective. In addition, previous case reports and case series have demonstrated that adnexal involvement is common in EMPD and that the adnexa may serve as a pathway for carcinoma spreading to deeper tissues where local therapeutic agents are less likely to be effective.[7,20,21] Since the depth of adnexal involvement has never been previously studied, our primary goal was to establish the depth of spread of carcinomatous cells along the adnexa in primary EMPD, and also to identify previously undescribed patterns of adnexal involvement by studying 178 lesions from 146 patients with primary anogenital EMPD.

MATERIAL AND METHODS

Case Selection

A search in the consultation, routine institutional, and personal files of the authors between 1993 and 2015 years yielded 167 cases coded as EMPD. Histological slides were reviewed along with the available clinical information obtained from patients' medical records to confirm the

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The authors declare no conflicts of interest.

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location and the clinicopathological context. Only cases of primary anogenital EMPD were included. Excluded from the study were 21 cases of secondary EMPD arising from carcinomas of other possible origins (rectum, urethra, prostate, etc.) as well as cases with insufficient clinical data. Thus, the study cohort consisted of 178 specimens from 146 patients with primary anogenital EMPD.

Light Microscopy

The study was based on the assessment of hematoxylin and eosin–stained slides, periodic acid-Schiff–stained and/or mucicarmine-stained sections, and immunostains for cytokeratin 7. Of the 178 specimens, 99 were wide surgical excisions, local resections, or vulvectomies (the number of tissue blocks ranged from 1 to 59; median 10) and 79 were small specimens (punch, or small incisional biopsies, with a single block per case). From 13 patients, both primary and recurrent tumors were available for study (1 recurrence in 8 patients; 2 recurrences in 4 patients; 3 recurrences in 1 patient).

Involvement of cutaneous adnexal structures including hair follicles, sebaceous, apocrine, and eccrine glands and their ducts were evaluated. Eccrine and apocrine ducts are typically indistinguishable, but in many cases their nature could be reasonably determined when they were clearly related to an underlying apocrine or eccrine secretory coil or acrosyringium (the intraepidermal part of the eccrine duct). When it was not possible to distinguish between apocrine and eccrine ducts, they were designated as "ducts, not otherwise specified". We also determined the presence and nature of involvement of AGMLG and their ducts, but these results will be the subject of a separate report.

Depth of invasion was determined on hematoxylin and eosin–stained slides from large resection specimens only (n = 99), whereas for small specimens (n = 79), only the frequency and distribution of adnexal involvement was documented. An ocular micrometer was used to measure the depth from the surface of the epidermis (cornified layer) or epithelium to the deepest located tumor cell in an involved adnexal structure. In all cases, we determined if there was microinvasion (defined as stromal invasion to a depth of no more than 1 mm below the basement membrane[22]) or if depth of invasion exceeded 1 mm. Twelve lesions were the subject of 2 previous reports.[23,24]

TABLE 1. Main Clinical Characteristics of 146 Study Patients

Parameter	N (%)
Age (yrs)	40–95 (median 73, mean 71.26)
Gender	
Female	114 (78.1)
Male	32 (21.9)
Location	
Genital	123 (84.2)
Vulva NOS or predominantly	93
Labium majus	8
Mons pubis	8
Scrotum (predominantly)	13
Periclitoral	1
Groin	10 (6.8)
Perianal	9 (6.2)
Anogenital, NOS	4 (2.7)

NOS, not otherwise specified.

RESULTS

Clinical Data

The clinicopathological features of the 146 patients are summarized in Table 1. There were 114 women and 32 men. Age at diagnosis (known in 142 patients) ranged from 40 to 95 years (median, 73 years; mean, 71 years). In all but 1 case, the lesions were solitary and occurred in the anogenital area sometimes involving large areas (eg, vulva and perianal area; scrotum and groin). One patient presented with bilateral groin lesions. In women, EMPD most commonly involved the vulva (89.4%) and less frequently the perianal (5.3%) regions. In men, EMPD mostly involved the scrotum (40.6%) and groin (25%). Thirteen patients had recurrences of EMPD. In a further 2 patients with recurrent EMPD, the slides of the original biopsies were not available for review. Clinically, most lesions appeared as flat or slightly elevated

FIGURE 1. Clinical appearance of extramammary Paget disease: Erythematous erosive areas.

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TABLE 2. Frequency and Depth of Invasion of Adnexal Structures in 99 Large Postoperative Specimens

Type of Adnexa	Involved/Present (% with Involved Adnexa); {Number/ % of Cases Where it was the Deepest Involved Structure}	Depth of Adnexal Involvement in mm
Hair follicles	91/98 (92.8); {76/83.5}	0.5–3.25 (median 1.6, mean 1.64)
Sebaceous glands	29/79 (36.7); {1/3.4}	0.4–1.5 (median 1, mean 0.98)
Eccrine secretory coil	12/95 (12.6); {5/41.7}	0.8–3.2 (median 2.55, mean 2.39)
Apocrine secretory coil	1/60 (1.7); {0}	1.8 (median 1.8, mean 1.8)
Adnexal ducts		
Eccrine ducts		
Acrosyringium	87/89 (97.7)	
Straight/coiled	54/76 (71.1); {13/24.1}	0.3–3.6 (median 1.1, mean 1.28)
Apocrine ducts	6/41 (14.6); {0}	0.5–1.38 (median 0.93, mean 0.99)
Ducts, NOS	14/72 (19.4); {1/7.1}	0.4–2.5 (median 0.94, mean 0.98)

NOS, not otherwise specified.

erythematous or white-gray areas, with variable scaling, excoriations, oozing, or crusting (Fig. 1).

Histopathological Findings

Of the 178 specimens, 165 were in situ EMPD and 13 were invasive EMPD. Of the latter, 9 were minimally invasive, as defined above, and 4 had dermal invasion >1 mm in depth. Inguinal lymph node metastases occurred in 1 case only.

Adnexal involvement was a common finding in large samples (Table 2) as well as in small biopsy specimens (Table 3). The most common targets were hair follicles, involved in 92.8% of large resection specimens (91 of 98

TABLE 3. Frequency of Invasion of Adnexal Structures in 79 Small Biopsies Specimens

Type of Adnexa	Involved/Present (% With Involved Adnexa)
Hair follicle	35/56 (62.5)
Sebaceous glands	5/23 (21.7)
Eccrine glands	1/44 (2.3)
Apocrine glands	1/9 (11.1)
Adnexal ducts	
Eccrine ducts	
Acrosyringium	23/26 (88.5)
Straight/coiled	7/21 (33.3)
Apocrine ducts	1/4 (25)
Ducts NOS	8/34 (23.5)

NOS, not otherwise specified.

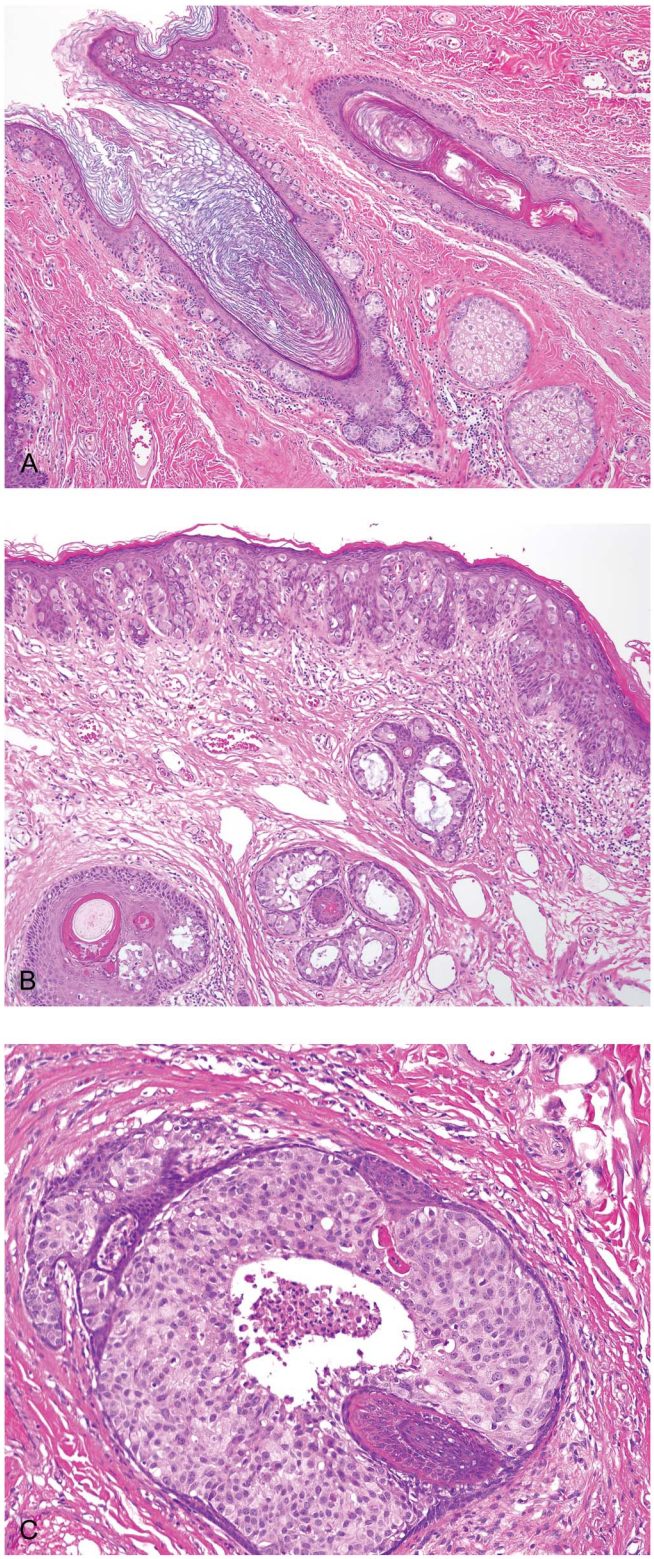

FIGURE 2. Involvement of hair follicles in EMPD. Single tumor cell infiltration and clusters of neoplastic cells involve a hair follicle (A). Gland-like structures in hair follicles, some with cribriform appearances, replacing most of native follicular epithelium (B). Prominent involvement of hair follicle with comedonecrosis (C).

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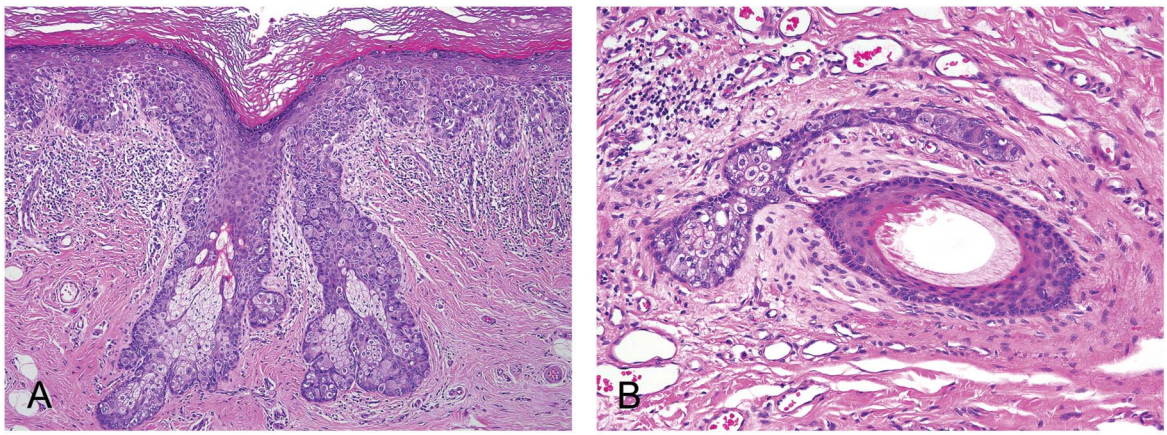

FIGURE 3. Involvement of sebaceous glands in EMPD. Dispersed single tumor cells and small clusters in mature sebaceous glands (A) and in the mantle (B).

specimens). In 76 large specimens (76.7%), the hair follicle was the adnexal structure most deeply involved (compared with sebaceous glands and apocrine or eccrine units). The maximal depth of carcinoma cells affecting hair follicles was 3.25 mm. In small biopsy specimens (n = 79), hair follicles were present in more than half of the cases, of which 62.5% (35/56) were involved by Paget cells. In most cases, neoplastic cells were dispersed in the affected hair follicles as single cells or small clusters (Fig. 2A). Less commonly, gland-like structures were formed (Fig. 2B). Whereas in most cases only a minor proportion of the native follicular epithelium was replaced by the neoplastic cells, a few cases demonstrated extensive follicular involvement by the carcinoma, sometimes accompanied by comedonecrosis (Fig. 2C).

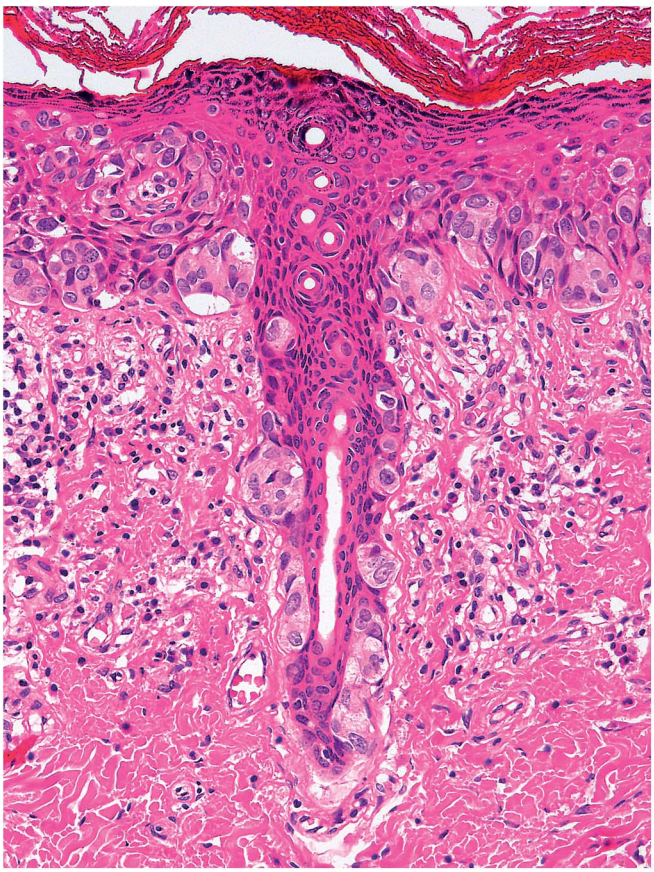

FIGURE 4. Infiltration of the acrosyringium in EMPD.

Sebaceous glands were infiltrated by Paget cells in a third of the large specimens and in a quarter of the small biopsy samples. Both mature sebaceous glands and mantles were seen to be involved by single cell spread or by small groups of tumor cells (Fig. 3), sometimes identified only after mucicarmine staining. The deepest involved sebaceous gland was located 1.5 mm below the stratum corneum.

Involvement of eccrine units most frequently manifested as infiltration of the acrosyringium (97.7%), which is logical due to its intraepidermal location (Fig. 4). Intradermal straight and coiled eccrine ducts were found in 76 large specimens and were infiltrated by tumor cells in 54 samples (71.1%) (Fig. 5), with the deepest involvement of 3.6 mm seen in 13 specimens. In most, there was single cell infiltration of the ducts but small clusters of neoplastic cells and gland-like structures were also noted less frequently (Fig. 6). Immature squamous cell metaplasia and hyperplasia of duct epithelium were occasionally encountered, and a combination of metaplasia and hyperplasia resulted rarely in cribriform formations (Fig. 7). In some cases, neoplastic cells were observed to have replaced mostly the basal/myoepithelial cells with the focal preservation of luminal cells (Fig. 8).

The eccrine secretory coils were infiltrated less frequently by tumor cells (12.6% of large specimens), in 4 cases showing the deepest involvement to be at a maximal depth of 3.2 mm. Similar to other adnexal structures, eccrine glands were seen to be colonized by single cells or groups of neoplastic cells, and rarely by gland-like structures. In some eccrine coils, complete replacement of the normal luminal epithelium by solid or cribriform formations of Paget cells, in the presence of preserved peripheral basal/myoepithelial cell layers, occasioned a resemblance to either ductal carcinoma in situ or so-called lobular cancerization as seen in mammary carcinomas (Fig. 9).

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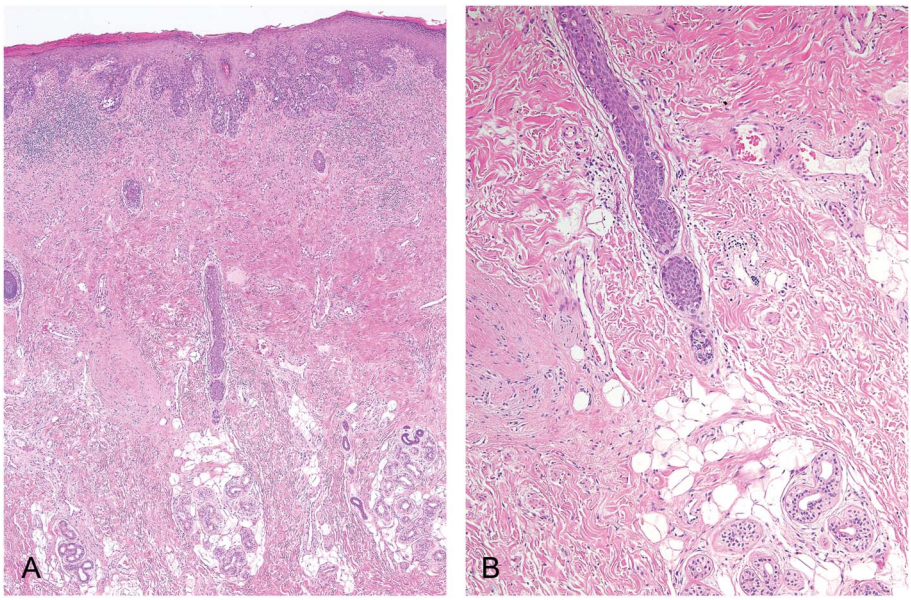

FIGURE 5. Involvement of the straight portion of eccrine duct in EMPD, mostly occurring as single cell colonization (A, B).

The apocrine secretory coils were involved in 14.6% of cases, and never were they the deepest structure affected by the carcinoma.

In 1 case, a large complex structure of uncertain derivation was involved by neoplastic cells (Figs. 10, 11), whereas in another case of recurrent EMPD involving the neovulva, carcinoma cells colonized the remnants of a Bartholin gland at a depth of 12 mm.

DISCUSSION

Our study validates the previously published observations that involvement of adnexa is a common feature in primary EMPD, likely contributing to the spread of carcinoma into deeper tissues and to the propensity for recurrence.[7,18,20,21,25] Our study contributes novel data by documenting the depth of adnexal involvement, hitherto not previously examined. We found that Paget cells may spread along the adnexa as deeply as 3.6 mm, with hair follicles and eccrine ducts/glands being the most commonly and the most deeply involved structures. This information should be taken into account when planning topical nonsurgical treatment or when developing new local treatment modalities in the future. At present, imiquimod, 5-fluorouracil, and retinoic acid are used in the treatment of EMPD attempting to substitute for alternative, often disfiguring surgical approaches. Other novel treatments including CO_2 laser, trastuzumab, alone or in combination with chemotherapy, and photodynamic therapy are being studied.[26–29] The above treatment modalities have differing mechanisms of action (eg, imiquimod acts as an immune response modifier; 5-fluorouracil is a chemotherapeutic agent; photodynamic therapy relies on light activation of a photosensitizer in neoplastic cells) but the depth of skin penetration and knowledge of the depths of tumor deposits

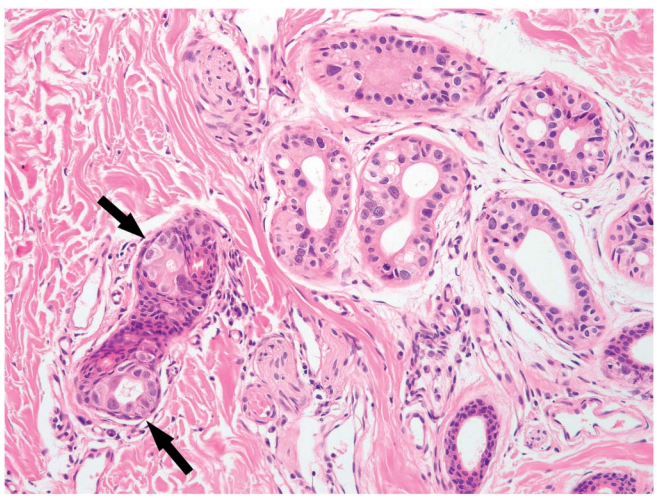

FIGURE 6. Gland-like structures in an involved eccrine duct (arrow).

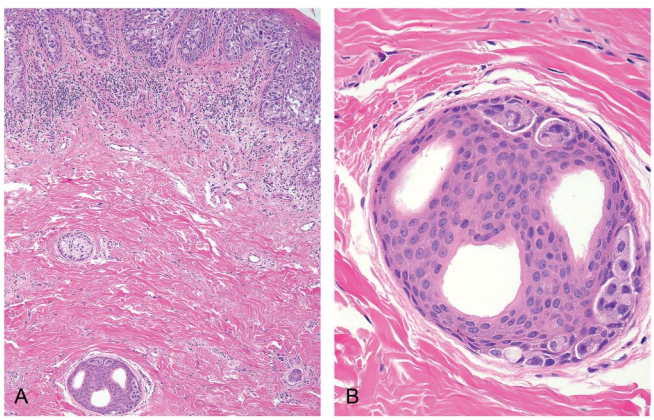

FIGURE 7. Carcinoma cell infiltration of an eccrine duct, which also shows squamous metaplasia and hyperplasia resulting in a cribriform appearance.

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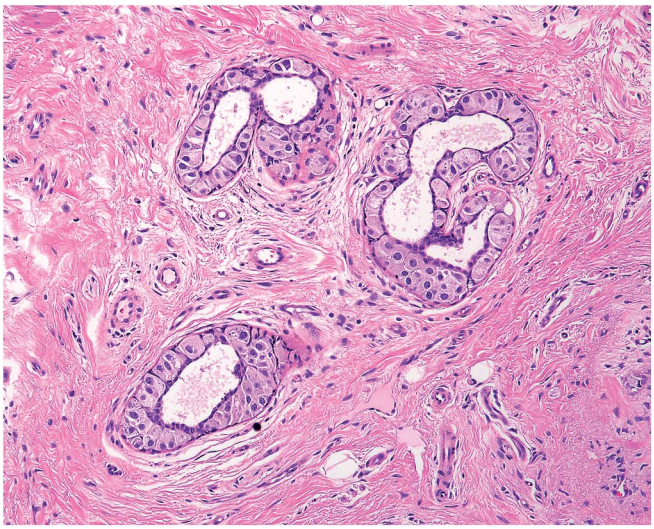

FIGURE 8. A duct showing replacement of the basal/myoepithelial cells by Paget cells.

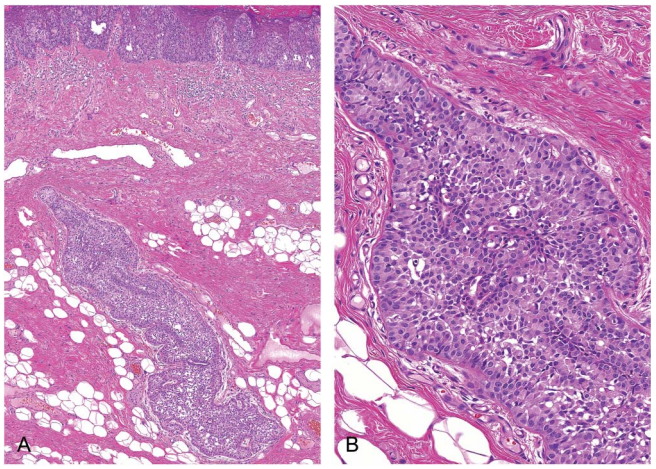

FIGURE 10. A large complex structure of uncertain derivation involved by neoplastic cells (A, B). It clearly differs from hyperplastic eccrine or apocrine units and also from anogenital mammary-like glands depicted in Figure 11 for comparison.

are obviously essential for planning successful treatment. From our literature review, we have been unable to determine to what depth imiquimod may penetrate the skin, whereas 5-fluorouracil reportedly penetrates the skin to a depth of 1–2 mm.[30] This is manifestly insufficient for a substantial number of cases in which Paget cells extend well beyond this. Whereas data on the presence or absence of invasion are available in previously published trials, the issue of adnexal spread has not been properly addressed. Nonetheless, it has been speculated that therapeutic responses may be related to the depth of penetration of imiquimod such that thicker portions of an in situ lesion or tumor with extensive adnexal involvement or invasive disease may exhibit incomplete responses.[31]

Appendages may be colonized by neoplastic cells in different ways. We noted several patterns of adnexal involvement These include involvement or spread as single cells, small clusters, gland-like formations, substitution of luminal cells in ducts/coils with preserved peripheral basal/myoepithelial cells resulting in ductal carcinoma in situ–like appearances, or, conversely, predominant replacement of basal/myoepithelial cells. Additionally, ductal structures may exhibit epithelial metaplasia and hyperplasia, posing potential diagnostic pitfalls. We also noted changes in AGMLG, structures mooted to play a role in the etiology and pathogenesis of primary EMPD,[7,2,3] but these results will be reported in a separate study.

In conclusion, adnexal involvement in primary EMPD is a very common feature occurring in more than 90% of cases. Hair follicles and eccrine ducts are the most commonly affected adnexa by Paget cells. In this study, the maximal depth of involvement was as much as 3.6 mm, with the median for each adnexal structure ranging from 0.93 mm (eccrine ducts) to 2.55 mm (eccrine secretory coils). Given the fact that we used for formalin-fixed tissues in the study, the actual depth of invasion in vivo is bound to be deeper. This phenomenon should be taken into account when planning topical therapy or developing novel local treatment modalities for EMPD.

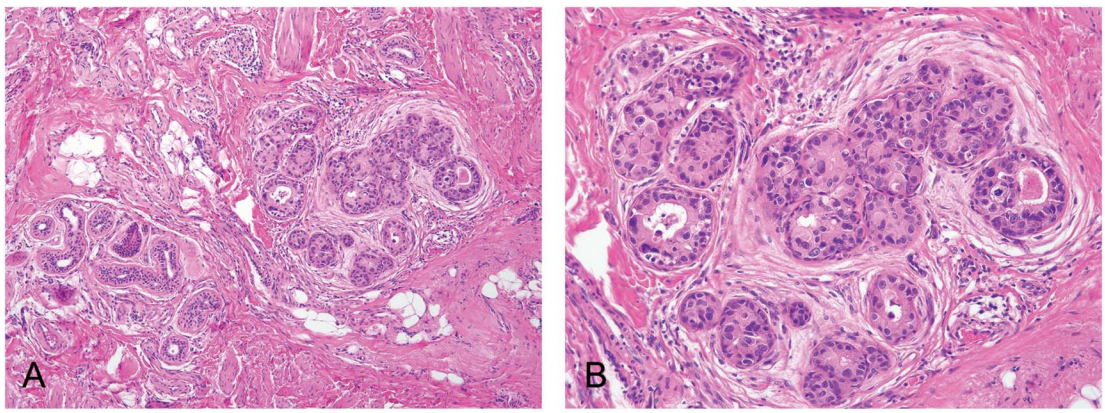

FIGURE 9. Infiltration of eccrine coils occasioning a resemblance to either ductal carcinoma in situ or so-called lobular cancerization as seen in mammary carcinomas (A, B).

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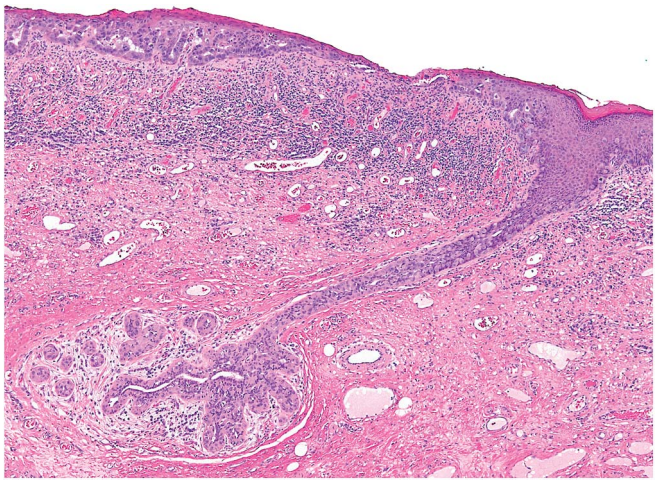

FIGURE 11. Anogenital mammary-like gland involved by carcinoma cells.

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